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Synthesis of indolylalkylphosphonates and 3-(1-diphenylphosphinoalkyl) indoles by reaction of 3-(1-arylsulfonylalkyl) indoles with phosphorus derivatives

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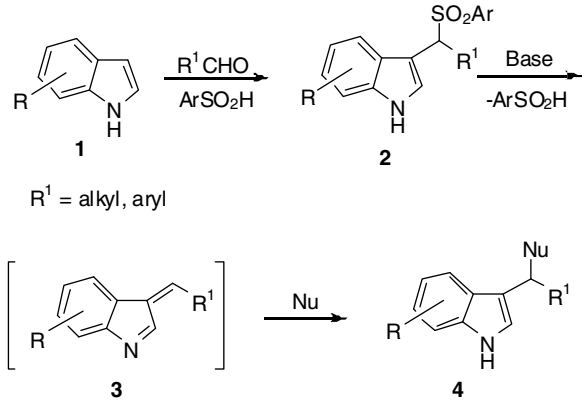
ABSTRACT

Dialkyl phosphites as well as diphenylphosphine react with 3-(1-arylsulfonylalkyl) indoles under basic conditions leading to a formal substitution of the arylsulfonyl group through a reactive 3-alkylidene indole intermediate.

The base-promoted hydrophosphonylation of electrophilic compounds represents a viable procedure to introduce a phosphonyl group into a wide array of functionalized substrates. According to this synthetic strategy, α-hydroxy as well as α-aminophosphonates can be readily prepared using aldehydes and imino derivatives as electrophiles.[1] Although less explored, conjugate addition of dialkyl phosphites to electron-poor olefins also represents a viable procedure to obtain β-phosphonylated derivatives.[2] In this context, the utilization of vinylogous imino derivatives in the reaction with dialkyl phosphites usually provides α-aminoalkenyl phosphonates through a regioselective 1,2-addition reaction.[3] Phosphonic acid derivatives can replace the more popular carboxylic group in many pharmaceutical targets introducing a consistent modification in their biological activity.[4] Furthermore, arylphosphonic acids have recently emerged as an important class of useful catalysts amenable of promoting enantioselective as well as many other synthetic processes.[5] Recently, we have demonstrated that 3-(1-arylsulfonylalkyl) indoles **2** readily obtained by a three-component coupling from indoles **1** are effective precursors of vinylogous-type imino derivatives **3** that regioselectively add nucleophilic reagent at the exocyclic double bond leading to the corresponding substituted indoles **4** (Scheme 1).[6]



Scheme 1.

Organometallic reagents as well as stabilized carbanions can be efficiently used as nucleophiles in this process, thus providing a straightforward synthesis of branched indole derivatives. The utilization of dialkyl phosphites **7** as heteronucleophiles in the reaction with sulfonyl indoles **6** is also successful in providing the corresponding indolylalkylphosphonates (Scheme 2, Table 1).

Indoles bearing an alkylphosphonyl substituent at 3-position are featured by a consistent pharmacological activity.[7] Furthermore, such derivatives are also pivotal intermediates in

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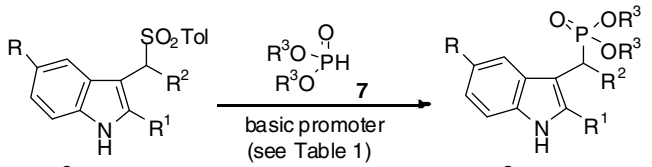


6a R = H; R^1 = H; R^2 = $PhCH_2CH_2$
6b R = H; R^1 = Me; R^2 = $PhCH_2CH_2$
6c R = H; R^1 = Me; R^2 = *c*-C_6H_{11}
6d R = H; R^1 = H; R^2 = *n*-C_5H_{11}
6e R = H; R^1 = Ph; R^2 = *n*-C_5H_{11}
6f R = H; R^1 = Ph; R^2 = Et
6g R = MeO; R^1 = H; R^2 = Et
6h R = H; R^1 = CO_2Et; R^2 = Et

7a R^3 = Et
7b R^3 = Me

Scheme 2.

Table 1
Synthesis of indolylalkylphosphonates **8** by reaction of 3-(1-arylsulfonylalkyl) indoles **6** with dialkyl phosphites **7**

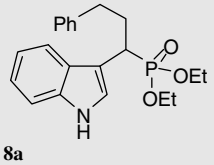
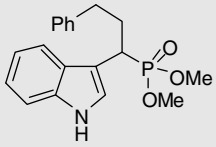
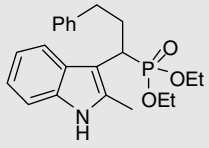
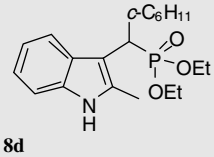
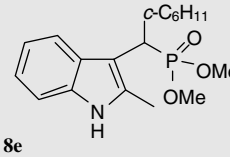
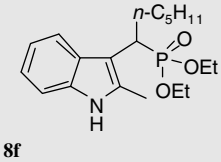
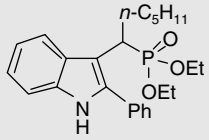
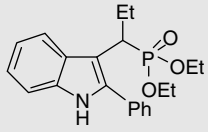
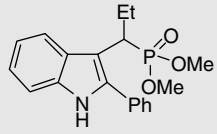
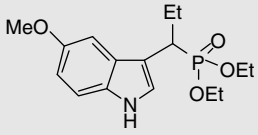
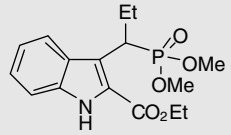
Entry	Sulfone **6**	Phosphonate **7**	Products[a] **8**	Yield[b] (%) (Method)[c]
1	**6a**	**7a**	 **8a**	65 (A)
2	**6a**	**7b**	 **8b**	66 (A)
3	**6b**	**7a**	 **8c**	68 (A)
4	**6c**	**7a**	 **8d**	70 (A)
5	**6c**	**7b**	 **8e**	75 (B)
6	**6d**	**7a**	 **8f**	77 (B)

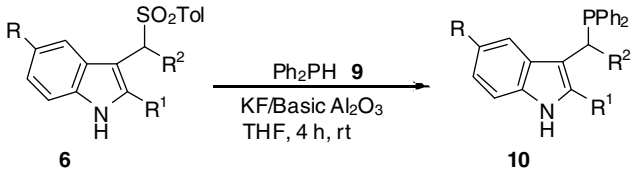
Table 1 (*continued*)

Entry	Sulfone **6**	Phosphonate **7**	Products[a] **8**	Yield[b] (%) (Method)[c]
7	**6e**	**7a**	 **8g**	88 (B)
8	**6f**	**7a**	 **8h**	84 (B)
9	**6f**	**7b**	 **8i**	76 (B)
10	**6g**	**7a**	 **8j**	80 (B)[d]
11	**6h**	**7b**	 **8k**	66 (A)

[a] All products were identified on the basis of their IR and NMR spectra.
[b] Yields of pure products isolated by column chromatography.
[c] *Method A*: dialkyl phosphite (1.5 mmol), NaH (2 mmol) in THF (10 mL), and sulfonyl indole (1 mmol) 2 h at rt. *Method B*: dialkyl phosphite (1.5 mmol), KF/basic alumina (2 g) in THF (5 mL), and sulfonyl indole (1 mmol) 15 h at rt.
[d] Reaction time 3 h.

the synthesis of biologically active compounds.[8] Potassium fluoride on basic alumina at room temperature acts as an efficient basic promoter for the addition of dialkyl phosphites **7** to sulfonyl indoles **6** (method B). The utilization of KF/basic alumina as promoter introduces a considerable simplification in the work-up procedures. Indeed, after removal of the solvent, the resulting solid mixture can be directly applied on the head of a chromatographic column for the final purification. However, we observed that for some substrates this heterogeneous basic system is not completely satisfactory since the starting material is still present in the reaction mixture even after prolonged reaction time. For these runs, sodium hydride in tetrahydrofuran is more effective than the former promoter (method A).

Good to excellent results are obtained with sulfonyl indoles **6** tested for this process (Table 1).[9] Steric crowding in close proximity to the reaction center does not usually affect the efficiency of the addition as evidenced for the utilization of sulfonyl indole **6c** bearing a cyclohexyl group at 1′ position (Table 1, entries 4 and 5). Similarly, the presence of a phenyl group at 2-position of the indole ring in compounds **6e,f** looks even beneficial in providing good yields of the phosphonylated products **8g–i** (Table 1, entries 7–9). Of particular interest is the reaction of sulfonyl indole **6h**



6a R = H; R^1 = H; R^2 = $PhCH_2CH_2$
6c R = H; R^1 = Me; R^2 = *c*-C_6H_{11}
6e R = H; R^1 = Ph; R^2 = *n*-C_5H_{11}
6f R = H; R^1 = Ph; R^2 = Et

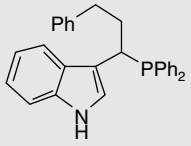
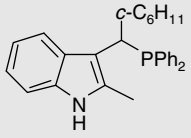
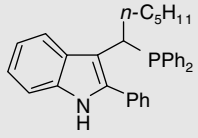
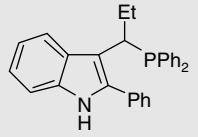
Scheme 3.

obtained from ethyl 2-indolecarboxylate with phosphonate **7b**, which affords indole **8k** bearing two ester functions of different acidic systems. Such derivatives are important structural analogues of glutamic and glutaric acids, which can be used in biological assays.[10]

The widespread interest in the preparation of trisubstituted phosphines prompted us to exploit the feasibility of a related process involving the utilization of diphenylphosphine as nucleophile in the reaction with sulfonyl indoles **6**.[11] Thus, diphenylphosphine **9** efficiently adds to sulfonyl indoles **6** in the presence of KF/basic alumina leading to the corresponding trisubstituted phosphines **10** in excellent yields (Scheme 3, Table 2).[12] The reaction conditions adopted for the addition of phosphine **9** are surprisingly mild, considering that the conjugate addition of **9** to enoates and amides usually requires the utilization of the corresponding lithium salt.[13]

In conclusion, 3-alkylidene indoles, generated under basic conditions from sulfonyl indoles **6**, react with dialkyl phosphites and diphenylphosphine leading to the corresponding adducts. Sodium hydride or potassium fluoride on basic alumina can be used as basic promoters showing different levels of efficiency depending on the heteronucleophile employed. The obtained phosphonates **8** may be considered as synthetic analogues of carboxylic acids or esters with potential biological activity.

Table 2
Synthesis of 3-(1-diphenylphosphinoalkyl) indoles **10** by reaction of 3-(1-arylsulfonylalkyl) indoles **6** with diphenyl phosphine **9**[a]

Entry	Sulfone **6**	Products[b] **10**	Yield[c] (%)
1	**6a**	 **10a**	88
2	**6c**	 **10b**	90
3	**6e**	 **10c**	86
4	**6f**	 **10d**	95

[a] Diphenylphosphine (1.1 mmol), KF/basic alumina (2 g) in THF (5 mL), and sulfonyl indole (1 mmol) 4 h at rt.
[b] All products were identified on the basis of their IR and NMR spectra.
[c] Yields of pure products isolated by column chromatography.

Acknowledgments

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9. *General procedure for the preparation of indolylalkylphosphonates* **8**. *Method A*: To a stirred suspension of NaH (2.0 mmol) in dry THF (10 mL), dialkyl phosphite **7** (1.5 mmol) was added at room temperature. After stirring at the same temperature for 20 min, sulfonyl indole **6** dissolved in dry THF (5 mL) was added dropwise. After stirring at room temperature for 2 h, the reaction mixture was quenched with satd. NH_4Cl (4 mL) and the resulting solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was then dried over $MgSO_4$ and after removal of the solvent at reduced pressure, the crude indolylphosphonate was purified by column chromatography (chloroform–methanol, 9:1). *Method B*: To a stirred solution of dialkyl phosphite **7** (1.5 mmol) and sulfonyl indole **6** (1 mmol) in THF (5 mL), KF on basic alumina [2 g, prepared from basic alumina (Baker, grade I) following the Bergbreiter's procedure][14] was added at room temperature. After stirring for the appropriate time, silica gel (0.8 g) was added and solvent was removed at reduced pressure. The solid mixture thus obtained was directly charged on a chromatographic column and eluted to afford pure indolylphosphonates. Selected data of compounds prepared: compound **8a**: Oil. IR (cm^{-1}, neat): 3648, 1280, 1170. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.96 (t, 3H, *J* = 6.8 Hz), 1.25 (t, 3H, *J* = 6.8 Hz), 2.25–2.39 (m, 1H), 2.40–2.53 (m, 2H), 2.62–2.73 (m, 1H), 3.34 (ddd, 1H, *J* = 3.8, 11.1, 22.2), 3.52–3.62 (m, 1H), 3.78–3.85 (m, 1H), 3.96–4.21 (m, 2H), 7.02–7.25 (m, 8H), 7.36 (d, 1H, *J* = 8.1 Hz), 7.58 (d, 1H, *J* = 7.7 Hz), 9.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3 (d, ^3J(CP) = 5.3 Hz, CH_3CH_2O), 16.5 (d, ^3J(CP) = 5.3 Hz, CH_3CH_2O), 31.8, 33.6, 34.3 (d, ^1J(CP) = 141.9 Hz, *CHP*), 61.8 (d, ^2J(CP) = 7.6 Hz, CH_3CH_2O), 62.6 (d, ^2J(CP) = 7.6 Hz, CH_3CH_2O), 109.4, 109.6, 111.6, 119.2, 119.4, 121.9, 123.8, 126.0, 127.7, 128.4, 128.6, 128.7, 136.1, 141.5. Compound **8g**: Oil. IR (cm^{-1}, neat): 3639, 1273, 1176. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.67 (t, 3H, *J* = 6.9 Hz), 0.95–1.15 (m, 9H), 1.24 (t, 3H, *J* = 7.3 Hz), 1.91–2.06 (m, 1H), 2.21–2.40 (m, 1H), 3.49 (ddd, 1H, *J* = 3.8, 11.1, 23.5 Hz), 3.75–3.84

(m, 1H), 3.87–4.03 (m, 2H), 4.09–4.20 (m, 1H), 7.08 (t, 1H, J = 7.3 Hz), 7.16 (t, 1H, J = 7.3 Hz), 7.35–7.50 (m, 4H), 7.65–7.69 (m, 2H), 8.01 (d, 1H, J = 8.1 Hz), 8.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 16.4 (d, ^3J(CP) = 5.3 Hz, CH_3CH_2O), 16.6 (d, ^3J(CP) = 5.3 Hz, CH_3CH_2O), 22.5, 27.3, 27.5, 28.2, 31.3, 36.1 (d, ^1J(CP) = 142.7 Hz, *CH*P), 61.7 (d, ^2J(CP) = 7.1 Hz, CH_3CH_2O), 61.8 (d, ^2J(CP) = 7.1 Hz, CH_3CH_2O), 61.9, 62.0, 62.3, 62.4, 110.9, 119.6, 122.12, 128.1, 128.3, 128.7, 128.9, 129.1, 133.1, 136.3, 137.3, 137.5. Compound **8h:** Oil. IR (cm^{-1}, neat): 3645, 1277, 1179. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.70 (t, 3H, J = 7.3 Hz), 1.07 (t, 3H, J = 7.3 Hz), 1.23 (t, 3H, J = 6.9 Hz), 2.05–2.18 (m, 1H), 2.21–2.38 (m, 1H), 3.40 (ddd, 1H, J = 4.3, 11.6, 23.5 Hz), 3.71–3.80 (m, 1H), 3.82–4.04 (m, 2H), 4.07–4.20 (m, 1H), 7.09 (t, 1H, J = 6.8 Hz), 7.16 (t, 1H, J = 6.8 Hz), 7.38–7.51 (m, 4H), 7.63–7.66 (m, 2H), 8.02 (d, 1H, J = 8.1 Hz), 8.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.7, 12.9, 16.5 (d, ^3J(CP) = 5.3 Hz, CH_3CH_2O), 16.6 (d, ^3J(CP) = 5.3 Hz, CH_3CH_2O), 21.8, 38.1 (d, ^1J(CP) = 142.7 Hz, *CH*P), 61.7 (d, ^2J(CP) = 7.6 Hz, CH_3CH_2O), 62.3 (d, ^2J(CP) = 7.6 Hz, CH_3CH_2O), 111.0, 119.5, 122.1, 128.1, 128.9, 129.2, 133.0, 136.3, 136.4. Compound **8k**: mp 144–146. IR (cm^{-1}, KBr): 3648, 1715, 1270, 1178. ^{1}H NMR (400 MHz, $CDCl_3$) δ: (mixture of rotamers) 0.82 (t, 1.5H, J = 7.2 Hz), 0.83 (t, 1.5H, J = 7.3 Hz), 1.30 (t, 1.5H, J = 7.3 Hz), 1.39 (t, 1.5H, J = 7.3 Hz), 2.20–2.38 (m, 1H), 2.40–2.56 (m, 0.5H), 2.57–2.65 (m, 0.5H), 3.53 (d, 1.5H, J = 10.7 Hz), 3.74 (d, 1.5H, J = 10.7 Hz), 3.77 (d, 1.5H, J = 11.3 Hz), 3.80 (d, 1.5H, J = 11.3 Hz), 4.11–4.22 (m, 2H), 4.26–4.40 (m, 2H), 4.57–4.67 (m, 0.5H), 5.60 (dd, 0.5H, J = 4.2, 11.5 Hz), 7.08–7.15 (m, 1H), 7.24–7.45 (m, 2H), 8.05–8.09 (m, 1H), 9.08 (s, 0.5H) 9.14 (s, 0.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.1, 12.9, 13.1, 14.5, 14.6, 20.4, 21.8, 22.4, 22.5, 36.6 (d, ^1J(CP) = 140.4 Hz, *CH*P), 52.8 (d, ^2J(CP) = 7.6 Hz, CH_3O), 53.1 (d, ^2J(CP) = 7.6 Hz, CH_3O), 61.1, 61.2, 65.3, 112.1, 112.3, 114.0, 120.5, 121.3, 123.8, 124.1, 125.8, 125.9, 128.9, 129.2, 135.7, 136.1, 136.3, 144.2, 161.2, 162.2.

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12. *General procedure for the preparation of 3-(1-diphenylphosphinoalkyl) indoles* **10**. Following the procedure reported in method B, diphenylphosphine **9** (1.1 mmol) and sulfonyl indole **6** (1 mmol) were made to react with KF on basic alumina (2 g) in THF (5 mL) for 4 h at room temperature. Selected data of compounds prepared: compound **10a:** Oil. IR (cm^{-1}, neat): 3642, 1423. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.01–2.11 (m, 1H), 2.20–2.31 (m, 1H), 2.40–2.48 (m, 1H), 2.71–2.79 (m, 1H), 3.76–3.81 (m, 1H), 6.91–7.60 (m, 18H), 7.73–7.76 (m, 2H), 9.53 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.7, 33.4 (d, ^3J(CP) = 13.0 Hz, CH_2Ph), 35.4 (d, ^1J(CP) = 71.0 Hz, *CH*P), 109.0, 111.6, 118.5, 119.2, 121.6, 124.8, 124.9, 126.2, 128.0, 128.1, 128.2, 128.4, 128.8, 128.9, 129.1, 130.8, 130.9, 131.2, 131.3, 131.5, 132.1, 132.6, 136.0, 141.2. Compound **10c**: mp 242–244. IR (cm^{-1}, KBr): 3648, 1428. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.69 (t, 3H, J = 6.8 Hz), 1.02–1.19 (m, 5H), 1.20–1.33 (m, 1H), 1.82–1.94 (m, 1H), 2.51–2.65 (m, 1H), 3.87 (dt, 1H, J = 3.0, 12.4 Hz), 7.00–7.42 (m, 12H), 7.45–7.59 (m, 4H), 7.73–7.82 (m, 2H), 8.23 (d, 1H, J = 7.7 Hz), 8.43 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.5, 27.7, 28.1, 28.3, 31.6, 39.1 (d, ^1J(CP) = 106.4 Hz, *CH*P), 110.7, 120.0, 122.4, 123.4, 127.8, 128.0, 128.2, 128.7, 128.9, 129.1, 131.0, 131.1, 131.3, 131.7, 131.8, 133.1, 133.4, 134.3, 136.3, 137.3, 137.5.
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